CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761164Orig1s000

SUMMARY REVIEW

Joint Supervisory Review for Regulatory Action

Date	November 11, 2020
From	Tanya Wroblewski MD (Cross-Discipline Team Leader, Division of Nonmalignant Hematology) Albert Deisseroth, MD, PhD (Associate Director, Division of Nonmalignant Hematology) Ellis Unger, MD (Director, Office of Cardiology, Hematology, Endocrinology, and Nephrology)
Subject	Joint Summary Review
BLA #	761164
Applicant	Bioverativ Therapeutics, Inc
Date of Submission	March 13, 2020
PDUFA Goal Date	November 13, 2020
Proprietary Name	ENJAYMO
Established or Proper Name	Sutimlimab
Dosage Form(s)	Injection: 1100 mg/22 mL (50 mg/mL)
Applicant Proposed Indication(s)/Population(s)	Treatment of hemolysis in adult patients with Cold Agglutinin Disease
Applicant Proposed Dosing Regimen(s)	Sutimlimab 6.5g (b) (4) or 7.5g (for patients ≥75kg), administered as an intravenous infusion over 1-2 hours once per week for the first 2 doses followed by every other week dosing
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s)	Treatment of hemolysis in adult patients with Cold Agglutinin Disease
Recommended Dosing Regimen(s)	As above.

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Glossary

ADA	Anti-drug antibody
ADaM	Analysis Data Model Implementation
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
AMR	Renal allograft antibody-mediated rejection
ANA	Anti-nuclear antibody
AR	Adverse reaction
BLA	Biologics license application
BP	Bullous pemphigoid
C1	Complement component 1
C1s	Complement subcomponent 1
CA	Cold agglutinin
CAD	Cold agglutinin disease
CAS	Cold agglutinin syndrome
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CIC	Circulating immune complexes
CMC	Chemistry, manufacturing, and controls
CMD	Complement mediated disorder
CP	Complement pathway
CR	Complete response
CSR	Clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DAT	Direct antiglobulin test
dsDNA	Double stranded DNA
DP	Drug Product
DS	Drug Substance
ECG	Electrocardiogram
EOT	End of treatment
EQ-5D-5L	5-Level EuroQol 5 Dimensions Questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
FMQ	FDA MedDRA query
GCP	Good clinical practice
Hgb	Hemoglobin
ICH	International Council for Harmonization
IgG4	Immunoglobulin G subclass 4
IND	Investigational New Drug Application
ITP	Immune thrombocytopenic purpura
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NHV	Normal healthy volunteer
NME	New molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PLI	Pre Licensing Inspection
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of [Fatigue] Severity
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per protocol
PRO	Patient reported outcome
PT	Preferred term
QOL	Quality of life
RBC	Red blood cell
REMS	Risk evaluation and mitigation strategy
RNP	Anti-ribonucleoprotein antibody
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Summary of clinical safety
SF-12	12-Item Short Form
ScL-70	Anti-scleroderma antibody
SLE	Systemic lupus erythematous
SOC	Systems organ class
SDTM	Study Data Tabulation Model
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
URI	Upper respiratory infection
USPI	United States Prescribing Information
UTI	Urinary tract infection
WAIHA	Warm autoimmune hemolytic anemia

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Benefit-risk information for the treatment of hemolysis in adult patients with Cold Agglutinin Disease (CAD) is derived from the results of global study BIVV009-03 Part A (the CARDINAL study). The CARDINAL study was a single-arm, open-label trial that included 24 adult patients with primary CAD who had at least one blood transfusion in the 6 months prior to enrollment, hemoglobin (Hgb) ≤10g/dL, and symptomatic disease. The primary composite endpoint was the proportion of patients that met a responder definition. In order to be classified as a responder, patients could not have received a blood transfusion from Week 5 through Week 26 and could not have received treatment for CAD beyond what was permitted per protocol. In addition, the patient's hemoglobin level at the assessment time point must have met either of the following criteria: Hgb level ≥12 g/dL or Hgb level increased by ≥2 g/dL from baseline. There was a screening/observation period of 42 days prior to baseline (Day 0). The baseline hemoglobin value was used to assess the primary endpoint, and baseline was defined as the last hemoglobin level before sutimlimab was initially administered. All 24 patients had hemoglobin assessed at days -42, -28, -14, and baseline.

Results from the prospectively planned primary composite endpoint and analyses of the individual components demonstrated a substantial response rate for patients with CAD. In total, 13 out of the 24 patients [54.2%, 95% confidence interval (CI): 32.8, 74.4] in the full analysis set met the responder criteria for the composite primary endpoint and the lower bound of the 95% CI of the response rate was >30%. The results for each of the components of the composite endpoint were also persuasive: 15 (62.5%) patients met the Hgb endpoint, 17 (70.8%) were transfusion-free from Week 5 to 26, and 22 (91.7%) patients did not receive protocol prohibited CAD medications. To further support efficacy, markers of hemolysis including lactate dehydrogenase (LDH) and bilirubin were measured. Among 14 patients with baseline and follow-up values, the mean bilirubin was 55 μmol/L [2.7-fold the upper limit of normal (ULN)] at baseline and 15 μmol/L (0.8-fold ULN) at the treatment assessment timepoint. Among 17 patients with baseline and follow-up values, the mean LDH decreased from 424 U/L (1.7-fold ULN) at baseline to 301 U/L (1.2-fold ULN) at the treatment assessment timepoint. The decrease in mean bilirubin and LDH values compared to baseline provide further evidence of decreased hemolysis. Based on the well understood natural history of CAD, improvements in Hgb, bilirubin, and LDH of this magnitude are unlikely to occur spontaneously.

The primary safety database consisted of 34 patients (30 patients with CAD, 3 with Cold Agglutinin Syndrome (CAS) and 1 with CAD/warm autoimmune hemolytic anemia (WAIHA). In general, the safety profile for sutimlimab was acceptable in a population comprised mostly of

elderly patients with multiple comorbidities and receiving concomitant medications. No patient discontinued therapy because of an adverse reaction (AR). Common ARs (>10%) reported in the CARDINAL study included; respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. In total, 6 of 24 (25%) patients experienced a serious adverse reaction. The most common type of serious adverse reaction was infections, reported in 3 of 24 (12.5%) of patients.

Given sutimlimab's mechanism of action, there is an increased risk of serious infections, including encapsulated organisms, in particular, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. In the primary safety population (N=34), 58.8% of patients experienced infections and 20.6% had a serious adverse event (SAE) of infection. Serious infections included: urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, staphylococcal wound infection, escherichia sepsis, acute cholecystitis, respiratory tract infection, and viral infection. No deaths were attributed to a treatment emergent adverse event (TEAE) of infection. Infections with encapsulated bacteria occurred in the clinical studies, including one patient with pneumococcal sepsis despite receiving a vaccination. No meningococcal infections were reported. No clear trend was observed comparing autoantibody positivity and overt symptoms of autoimmune disease, including systemic lupus erythematosus (SLE).

In summary, the trial results indicate that sutimlimab confers substantial benefits in terms of reduction in blood transfusions and increase in hemoglobin levels in patients with CAD. Improvements in LDH and bilirubin levels provide important, objective, mechanistic support for the efficacy findings. The safety profile of sutimlimab is acceptable. We believe that the single, baseline-controlled trial provides substantial evidence of effectiveness for this application, given the robust improvement in objective laboratory parameters that would be extremely unlikely to occur spontaneously in an untreated population with this disease. Flexibility is appropriate in the setting of this rare, serious, and chronic disease, especially because there are no FDA-approved therapies at this time.

Because of deficiencies identified at the [redacted] (b) (4) facility, however, this application cannot be approved at the present time, and a Complete Response will be issued. The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved because of deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection of the [redacted] (b) (4) drug substance manufacturing facility. Deficiencies included lack of quality oversight, significant data integrity concerns, and failure to conduct a comprehensive assessment to ensure accurate and reliable results submitted to the BLA.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cold Agglutinin Disease (CAD) is a type of autoimmune hemolytic anemia resulting from a clonal B-cell proliferative disorder of the bone marrow, which in turns activates the classical complement pathway. • The incidence is estimated at approximately 1 to 1.8 per million with a prevalence of approximately 13 to 16 per million, based on retrospective	CAD is rare, serious disease with chronic morbidities with many patients experiencing flares of hemolysis and anemia that can be severe.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reviews from Scandinavian countries. • This rare disease primarily affects middle-aged to elderly adults. Symptoms related to anemia such as fatigue, dyspnea, and weakness can substantially impair quality of life. In addition, patients often have symptoms such as acrocyanosis and may be at an increased risk for thromboembolic events.	
Current Treatment Options	• Treatment of CAD often consists of supportive therapies, including avoidance of cold, blood transfusions, and warming of blood during transfusions. • Other therapies used off-label include rituximab as monotherapy or in combination with cytotoxic agents; however, these may not be effective or durable and can be associated with significant toxicities. • Corticosteroids generally have no role in the treatment of CAD. • There are no approved therapies for CAD	There are no FDA-approved therapies for the treatment of CAD. There is an unmet medical need for an effective treatment for all patients with CAD in the United States. Treatments for CAD are needed because of high morbidity associated with this disease.
Benefit	• In a single-arm, open-label trial (BIVV009-03 Part A), 24 patients with symptomatic CAD and a recent blood transfusion received sutimlimab, administered on Days 0 and 7, followed by treatment every two weeks for 26 weeks. • 54.2% (95% CI: 32.8, 74.4) of patients met the responder definition: Hgb level ≥12 g/dL or increased by ≥2 g/dL from baseline, transfusion independence, no use of prohibited therapies. • In total, 62.5% of patients met the predefined Hgb endpoint (Hgb level ≥12 g/dL or Hgb level increased by ≥2 g/dL from baseline at the treatment assessment endpoint), 70.8% were transfusion-free from Week 5 to 26, and 91.7% of patients did not receive protocol-prohibited CAD medications. • Patients also demonstrated objective improvement in markers of hemolysis, i.e., decreases in LDH and bilirubin.	The CARDINAL study demonstrates that sutimlimab confers substantial benefits in terms of reduction in blood transfusions and increase in hemoglobin levels in patients with CAD. Improvements in LDH and bilirubin levels provide important, objective, mechanistic support for the efficacy findings. We believe that the single, baseline-controlled trial provides substantial evidence of effectiveness for this application, given the robust improvement in objective laboratory parameters that would be extremely unlikely to occur spontaneously in an untreated population with this disease. Flexibility is appropriate in the setting of this rare, serious, and chronic disease, especially because there are no FDA-approved therapies at this time.
Risk and Risk Management	• Primary safety results included 34 patients pooled from BIVV009-01 Part C&E and BIVV009-03 Part A and B. • The most common types (>10%) of TEAEs reported in the 24 patients in the pivotal study (BIVV009-03 Part A) were: respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia,	Overall, acceptable risk benefit profile. Risks of sutimlimab can be sufficiently addressed through Warnings and Precautions in the United States Prescribing Information (USPI).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	arthritis, and peripheral edema. • In the primary safety population, the most common type of treatment-emergent SAEs were infections, reported in 7 of 34 patients (21%). Serious infections included; urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, wound infection staphylococcal, escherichia sepsis, acute cholecystitis, respiratory tract infection, and viral infection. • Given the mechanism of action of the drug, patients may be at risk for infections caused by encapsulated organisms, in particular *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Infections from encapsulated bacteria were reported. One patient had pneumococcal sepsis despite receiving a vaccination. • There is a theoretical risk of autoimmunity with inhibition of early components of the classical complement pathway. No clear trend was demonstrated in studies with sutimlimab to date. • The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved because of deficiencies related to readiness for commercial manufacturing and data integrity observed at the FDA pre-license inspection of (b) (4) the facility responsible for the sutimlimab Drug Substance (DS) manufacturing process and quality control for release and stability testing of sutimlimab DS and Drug Product (DP): lack of quality oversight and significant data integrity concerns and failure to conduct a comprehensive assessment to ensure accurate and reliable results submitted to the BLA.	Long term safety will be assessed in a post marketing requirement. The data submitted in this application are not adequate to support the conclusion that manufacture of sutimlimab is well-controlled and leads to a product that is pure and potent. The recommendation from product quality is for a Complete Response for sutimlimab. A Complete Response action will be taken because of significant quality oversite deficiencies and data integrity issues at a commercial manufacturing site. Satisfactory resolution of the observations is required before this BLA may be approved.

2. Background

Product Information
Sutimlimab (BIVV009; TNT009) is a new molecular entity and is a humanized IgG4 monoclonal antibody that targets the classical complement pathway by inhibiting the CP-specific serine protease, complement component 1(C1), s component (C1s). The proposed dose regimen of sutimlimab is 6.5g (b) (4) or 7.5g (patients (b) (4), administered by intravenous (IV) infusion over 1-2 hours once per week for the first 2 doses followed by every other week thereafter.

The applicant is proposing sutimlimab for the treatment of hemolysis in patients with CAD.

Therapeutic Context
Cold Agglutinin Disease is a type of autoimmune hemolytic anemia that is caused by IgM-induced complement activation. CAD is diagnosed by the presence of IgM antibodies that agglutinate red blood cells (RBCs) at temperatures below normal body temperature, chronic hemolytic anemia, and its resultant symptoms. Chronic hemolysis is caused by the binding of cold agglutinin IgM antibodies to the I antigen, a glycoprotein membrane antigen universally present on RBCs. Binding of IgM antibodies to the I antigen results in the recruitment of activated complement fragments on the RBC, which leads to uptake and lysis of RBC by the reticuloendothelial system with intravascular hemolysis and anemia. The anemia can result in symptoms such as fatigue, dizziness, and dyspnea, and acrocyanosis. Chest pain, and Raynaud's syndrome are also reported. Patients are predisposed to thrombotic events. As complemented-coated RBCs are usually cleared through extravascular hemolysis and phagocytosis by liver macrophages, elevated total bilirubin is typical with the disease.

CAD is a rare disease that mostly affects middle-aged and elderly patients (median age of onset is 67 years). There is a female predominance, although this may be secondary to their longer lifespan. Patients with CAD can display varying levels of chronic hemolysis with episodes of hemolytic flares, exacerbating symptoms of fatigue, shortness of breath, and general weakness.

There are currently no FDA-approved therapies for the treatment of CAD. Treatments are considered if the patient develops symptomatic anemia or disabling cold-induced circulatory symptoms. Supportive nonpharmacologic therapies include keeping warm, avoidance of cold infusions, and blood transfusions. Folic acid and erythropoietin may be used as supportive therapies.

Corticosteroids and immunosuppressant drugs such as azathioprine or cyclophosphamide are not effective in CAD and should not be used for therapy. Splenectomy is not effective, which is expected as extravascular hemolysis is mostly localized to the liver. There has been some benefit with treatments targeting B-cell clones such as rituximab monotherapy, bortezomib and eculizumab, which is a C5 monoclonal antibody, but these are unapproved.

Sutimlimab blocks the activity of the C1s esterase, which is the proximal step in the activation of the classical pathway.

Regulatory Background

Sutimlimab is not currently approved in the US or any other country.

The following table, from the clinical review by Carrie Diamond, M.D., describes the regulatory interactions.

Table 1. Regulatory Interactions

Date	Regulatory Interaction
December 12, 2015	Pre-investigational new drug written responses were issued to discuss the clinical development program of sutimlimab, in particular to gain feedback on the design of the phase 1 study.
January 18, 2017	Study may proceed letter was issued for the phase 1 dose confirmation study in healthy volunteers under IND 128190.
May 30, 2017	End-of-phase 1 and initial comprehensive multidisciplinary breakthrough therapy meeting was held to discuss the registrational path for the treatment of hemolysis in patients with CAD. Agreement was reached regarding the proposed population, endpoints, and study duration of the pivotal Cardinal study.
March 23, 2018	Meeting to discuss the statistical analysis plan for the pivotal Cardinal Study (BIVV009-03 Part A).
December 10, 2018	Written comments were provided obtaining to the presentation of the anticipated BLA.
July 12, 2019	Pre-BLA meeting (written comments were provided).
September 26, 2019	Pre-BLA chemistry, manufacturing, and controls (CMC) meeting.
November 4, 2019	Pre-BLA meeting (written comments provided) to discuss the final components of the BLA submission and review topline data from the pivotal Cardinal study.
April 6, 2020	A type A meeting was held to discuss the integrity investigation pertaining to the sutimlimab BLA.

Orphan drug designation was granted on July 27, 2016 for the treatment of autoimmune hemolytic anemia.

Breakthrough therapy designation was granted on May 17, 2017 for the treatment of hemolysis

in patients with CAD.

Rolling submission components of the application were received as follows: Part 1, the non-clinical portion, was submitted September 5, 2019; Part 2, the clinical portion, was submitted February 26, 2020; and Part 3, the CMC and labeling, were submitted March 13, 2020. Priority review was granted at the time of filing.

3. Product Quality

This summary is taken from the Office of Product Quality (OPQ) review by Xiaoshi Wang, Viviana Matta, Maria Martin Manso, Yan Wang, Candace Gomez-Broughton, Maria (Reyes) Candau-Chacon, and Peter Qui.

The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved because of deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug substance manufacturing facility.

The data submitted in this application are not adequate to support the conclusion that manufacture of Enjaymo is well-controlled and leads to a product that is pure and potent. The recommendation from product quality is for a Complete Response for sutimlimab.

The OPQ inspection team issued an FDA Form 483 citing deficiencies and the recommendation for the (b) (4) site was withhold. Following a facility inspection, OPQ identified significant quality oversite deficiencies and data integrity issues that remain unresolved, resulting in a facility withhold recommendation. The PLI resulted in a final withhold decision for this BLA due to lack of quality oversight and significant data integrity concerns and failure to conduct a comprehensive data integrity assessment to ensure the accurate and reliable results submitted to the BLA application.

From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER does not note any product quality deficiencies that would preclude approval of STN761164 for Enjaymo (sutimlimab) manufactured by Bioverativ UAS Inc. at this time. Because this application will not be approved in this cycle, the manufacturing facility issues listed below will be directly communicated to (b) (4) because (b) (4) is a contract manufacturing organization (CMO). If manufacturing changes are made before the applicant submits their responses to the Complete Response deficiencies, additional assessment may be needed during the next assessment cycle.

- Potency and Strength:
  Sutimlimab is supplied as 50 mg/mL solution in one strength (i.e., 1100 mg/22 mL). Potency is defined as the percent activity relative to the current sutimlimab primary reference standard. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:

Sutimlimab is supplied as a sterile, single-dose, preservative-free solution for intravenous infusion in one strength. Each vial of 1100 mg/22 mL strength is filled with a target fill volume of (b) (4) mL.

- List of Excipients:
  10 mM sodium phosphate, 140 mM sodium chloride, pH 6.1, 0.02% (w/v) polysorbate 80, water for injection, pH 6.1.

- Container Closure System:
  The primary CCS for sutimlimab DP consists of a clear (b) (4) 25mL glass vial closed with a (b) (4) rubber stopper (b) (4). The rubber stopper is crimped to the vial with an aluminum overseal with (b) (4) cap.

- Dating Period and Storage Conditions:
  The dating period for the 1100 mg/22 mL strength DP is 18 months when stored at 2 to 8°C.

Microbial quality of the DS manufacturing process (b) (4) The raw material program, facilities and equipment, manufacturing process, release and stability programs are adequately controlled.

Review of the manufacturing identified that the methodologies used for the DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

(b) (4)

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology review was performed by Shaji Theodore, MVSc, PhD, DABT and C. Lee Elmore, PhD. They recommended approval. The summary below is taken from the non-clinical review by authors stated above.

The cynomolgus monkey was the only nonclinical species demonstrated to be pharmacologically relevant; therefore, the nonclinical program was conducted only in this species. A 26-toxicity study was conducted in cynomolgus monkeys that received intravenously administered sutimlimab at 60 and 180 mg/kg/week. Chronic administration of sutimlimab in monkeys led to

nearly complete inhibition of classical complement activity (up to 90% reduced activity) at both dose levels. The degree of complement inhibition was not dose-dependent. The duration of inhibition was prolonged at 180 mg/kg/week compared to 60mg/kg/week, consistent with other monoclonal antibodies, where saturation of target is achieved at lower doses and the duration of pharmacodynamic effect is extended at higher doses because of prolonged clearance. No sutimlimab-related adverse effects were observed up to the highest dose, which represents 5 times the clinical exposures at the 7.5-g clinical dose. No signals for increased infections were observed in non-clinical studies. Safety pharmacology endpoints incorporated into the repeat-dose toxicity study in monkeys did not identify any sutimlimab-related adverse effects on cardiovascular, respiratory, or central nervous system (CNS) endpoints at either dose. Anti-drug antibodies (ADA) developed in 2 of 10 animals at 60 mg/kg/week and 1 of 10 animals at 180 mg/kg/week. No adverse impacts on the health of animals were observed.

No genotoxicity studies were conducted with sutimlimab as monoclonal antibodies are generally considered devoid of mutagenetic or clastogenic risk. Given the absence of proliferative lesions observed at either dose tested in the chronic monkey study and the lack of any identified tumorigenic risk based on the mechanism of action and search of the relevant scientific literature, it is unlikely that sutimlimab possesses significant tumorigenic potential. CDER's Executive Carcinogenicity Assessment Committee concurred with this assessment and no additional studies of the carcinogenic potential of sutimlimab are warranted at this time.

An enhanced pre- and post-natal developmental (ePPND) toxicity study was conducted in pregnant monkeys with intravenous administration of 60 and 180 mg/kg/week sutimlimab to evaluate the potential for embryo-fetal and pre/postnatal developmental toxicity. There were no adverse effects on reproductive or development outcomes at doses higher than 180 mg/kg/week, which represents 4-times the human exposure at the 7.5-g dose. No dedicated fertility assessment was conducted with sutimlimab and no effects on reproductive tissues that would indicate the potential for sutimlimab to affect fertility were observed in the 26-week repeat-dose study in cynomolgus monkeys at doses up to 180 mg/kg/week.

In summary, based on a chronic toxicity study in monkeys in which monkeys received 5-times the clinical exposure at the 7.5-g dose, sutimlimab demonstrated robust and prolonged inhibition of C1s component. No significant adverse effects were observed. Sutimlimab is unlikely to have significant carcinogenic risk and no further carcinogenicity assessments are recommended at this time. In addition, sutimlimab did not cause adverse reproductive or developmental outcomes when administered to pregnant monkey up to 4-times the clinical exposure at the 7.5-g dose.

5. Clinical Pharmacology

Xiaolei Pan, Sudharshan Hariharan, Jihye Ahn, Justin C Earp, and Doanh Tran conducted the OCP review. They recommend approval of sutimlimab for the treatment of hemolysis in adult patients with CAD.

Sutimlimab is an immunoglobulin G (IgG), subclass 4 (IgG4) monoclonal antibody (mAB) that targets and inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease for C4. Inhibition of the classical

complement pathway at the level of C1s prevents deposition of complement deposition on the surface of RBCs, resulting in inhibition of hemolysis in patients with CAD. The proposed dosing regimen is 6.5 g or 7.5.g (based on body weight) administered intravenously.

The clinical development program includes three Phase 1 clinical pharmacology trials (i.e., single- and multiple-ascending dose, and Japanese bridging studies), and one Phase 3 efficacy/safety trial (CARDINAL). The submission also includes one report for the development of population pharmacokinetic (PPK) models for sutimlimab, and one report for the development of exposure-response relationship.

The applicant has submitted three Phase 1 clinical pharmacology studies, with several subparts in each of these studies covering single-ascending dose PK/PD in healthy volunteers, multiple-ascending dose PK/PD in healthy volunteers, single-dose and multiple-dose PK/PD in healthy Japanese volunteers, and a multiple-dose study in patients with a complement-mediated disorder including renal allograft antibody mediated rejection (AMR), BP (bullous pemphigoid), WAIHA (warm autoimmune hemolytic anemia), and CAD.

Population pharmacokinetic analysis was performed to evaluate the effect of intrinsic and extrinsic factors on sutimlimab pharmacokinetics. Summarized below are the key clinical pharmacology findings from the submitted studies:

Distribution

- Sutimlimab binds to C1s in the serum.
- The volume of distribution at steady-state was approximately 5.8 L in patients with CAD.

Elimination

- Sutimlimab clearance (CL) is governed by 2 parallel elimination pathways: a nonlinear, target mediated pathway predominating at low concentrations (20 - 100 μg/mL) and a nonspecific, linear pathway predominating at higher concentrations (>100 μg/mL).
- Linear CL is more predominant over the range of plasma concentrations achieved at the proposed dosing regimen. The population PK model predicted linear CL of sutimlimab at 5.65 mL/h (~0.14 L/day).
- The distribution and terminal elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively) of sutimlimab were 0.84 and 20.9 days, respectively, at the recommended dosage.

Metabolism

- Sutimlimab is a protein. It is generally recognized that antibodies are metabolized by degradation into small peptides and individual amino acids.

***Intrinsic Factors*:**

- Sex, age and race: No clinically significant differences in the pharmacokinetics of sutimlimab were observed based on sex, age (19 to 88 years old), and ethnicity (Japanese, non-Japanese).
- Body weight: Population pharmacokinetic analysis showed that sutimlimab exposures decreased up to 59% for a subject weighing 98 kg, and increased up to 57% for a subject weighing 50.5 kg as compared with a patient weighing 71.9 kg. The effect of body weight on

pharmacokinetics has been incorporated in the recommended dose regimen tiered by body weight.

- Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of sutimlimab are unknown.
- Renal impairment: Based on population PK data, no clinically significant differences in the pharmacokinetics of sutimlimab were observed based on mild to moderate renal impairment (30 to 89 mL/min/1.73 m^2 measured by estimated glomerular filtration rate [eGFR]). The effect of severe renal impairment on the pharmacokinetics of sutimlimab is unknown.

The following table is taken from the review by the clinical pharmacology team.

Table 2. General Pharmacology and Pharmacokinetics Characteristics

Pharmacology	
Mechanism of Action	Sutimlimab is an IgG4 mAb that inhibits the CP pathway and specifically binds to C1s, a serine protease which cleaves C4. Sutimlimab does not inhibit the lectin and alternative pathways. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement opsonins on the surface of red blood cells, resulting in inhibition of hemolysis in patients with CAD.
QT Prolongation	Large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions. A thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies.
General Information	
Bioanalysis	Two validated enzyme-linked immunosorbent assays (ELISA) were developed to measure the concentrations of sutimlimab in the serum/plasma samples collected from both patients and healthy subjects in the clinical studies included in this BLA. Semi-quantitative ELISA assays were developed to measure the PD response for sutimlimab, including CP and alternative pathway (AP) activity, PD biomarkers (C1q, C1s, CH50, C1sC1INH) concentrations, in the serum samples collected from both patients and healthy subjects. A validated quantitative LC-MS/MS method was developed to measure total C1s concentration in plasma sampled collected from patients in CARDINAL study. Three assays were developed to detect antidrug antibodies (ADAs) directed against sutimlimab. However, only two of the methods were validated with different reported sensitivity and drug tolerance.

Healthy Volunteers vs. Patients	PK was similar between CAD patients and healthy subjects	
Drug exposure at steady-state following the therapeutic dosing regimen	Based on the population analysis, the means (SD) of C_{min}, C_{max} and AUC_{tau} at steady state were 1516 (913) µg/mL, 3447 (1216) µg/mL, and 734627 (335279) µg*hr/mL, respectively.	
Minimal effective dose or exposure	The IC_{90} of sutimlimab for CP inhibition in vitro was ~ 63.9 µg/mL. In clinical trials, CP activities were consistently inhibited at concentrations above 100 µg/mL.	
Maximum tolerated dose or exposure	Single Dose	100 mg/kg sutimlimab was the highest dose tested; and maximum tolerated dose (MTD) was not achieved.
	Multiple Dose	75 mg/kg sutimlimab was the highest dose tested; and maximum tolerated dose (MTD) was not achieved.
Dose Proportionality	The mean $AUC_{0-\infty}$ increased in a greater than dose-proportional manner over the 3 to 30 mg/kg dose range, but increased in an approximately dose-proportional manner over the 60 to 100 mg/kg dose range (0.3 to 1.5 times the maximum approved recommended dosage based on 75 kg).	
Variability	The total variability of steady-state C_{trough} in CAD patients at the recommended dose regimen ranged from 39.6% to 78.6%. The inter-individual variability for linear CL and central volume of distribution was estimated as 34% and 21%, respectively, based on population PK analysis.	
Accumulation	Steady-state appeared to be achieved by Week 7. The accumulation ratios were determined to be 1.8 for AUC_{0-168h} and 1.5 for C_{max} following 75 mg/kg of sutimlimab doses on Days 1, 8, 22 and 36.	
Immunogenicity	• In part A of CARDINAL study, none of the 24 patients enrolled who received at least one dose of sutimlimab developed treatment-emergent ADAs. • In healthy subjects, 13% (4 out of 30 subjects) had confirmed ADAs on EOS days.	
Absorption		
T_{max}	Immediately following IV infusion	
Absolute bioavailability	Not applicable (N/A) as sutimlimab is administered IV infusion	
Distribution		

V_d	5.8 L
Protein Binding	N/A
Substrate of transporter systems	N/A
Elimination	
$T_{1/2}$	The terminal elimination half-life is 21 days
Primary elimination pathways	Catabolism in plasma
Metabolism	
Primary Metabolizing enzymes	Metabolized by degradation into small peptides and individual amino acids
Inhibitor/Inducer	N/A

General dosing

The recommended dose is 6,500 mg for patients weighing 39 kg to <75 kg, and 7,500 mg for patients weighing ≥75 kg. Sutimlimab is to be administered intravenously. The drug should be administered weekly for the first two weeks, and every other week thereafter.

If a dose is missed, administer as soon as possible; thereafter, resume dosing every two weeks. If the duration after the last dose exceeds 17 days, restart dosing weekly for two weeks followed by every other week dosing.

6. Clinical Microbiology

The microbiological quality of the proposed products is acceptable. Please refer to the OPQ review for additional details.

7. Clinical/Statistical—Efficacy

The clinical reviewer was Dr. Carrie Diamond M.D., and the statistical reviewers were Yaping Wang, PhD (Statistical Reviewer, DBIX) and Yeh-Fong Chen, PhD (Statistical Team Leader, DBIX). They recommend approval for this product. This review borrows heavily from their reviews.

Study BIVV009-03 (Cardinal study) was an open-label, single-arm, 2-part study: part A was designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with CAD and a recent history of blood transfusion. Part B is ongoing and will evaluate the long-term safety, tolerability, and durability of response of sutimlimab in patients with CAD.

In part A only, 24 patients with a diagnosis of CAD who had at least one blood transfusion in the 6 months prior to enrollment received weight-based doses of sutimlimab intravenously (6.5 g if body weight <75 kg; 7.5 g if body weight ≥75 kg) on days 0, 7, and biweekly thereafter, to day 175 (Week 25). Patients who missed a dose (>17 days) received an additional loading dose. End of treatment was defined as Day 182 (Week 26).

The study included patients ≥18 years of age with a confirmed diagnosis of CAD based on the following criteria; chronic hemolysis, polyspecific direct antiglobulin test (DAT) positive, monospecific DAT strongly positive for C3d, cold agglutinin titer ≥64 at 4°C, and IgG DAT ≤ 1+. In addition, patients must have had at least one blood transfusion in the preceding 6 months and hemoglobin ≤10 g/dL. Lastly, patients had to be symptomatic, defined as the presence of one or more signs or symptoms within 3 months of screening: symptomatic anemia, acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, and major adverse vascular events. Patients had a bone marrow biopsy 6 months prior to screening and were included if there was no overt evidence of lymphoproliferative disease or other hematological malignancy. Patients were excluded if they had cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy.

Primary Endpoint

The primary efficacy endpoint was responder rate, which was a composite endpoint. A patient was considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 (end of treatment) and did not receive treatment for CAD beyond what was permitted per protocol. Additionally, the patient's Hgb level must have met either of the following criteria:

- Hgb level ≥12 g/dL at the treatment assessment endpoint (defined as the mean value from Weeks 23, 25, and 26) or
- Hgb level increased by ≥2 g/dL from baseline (defined as the last hemoglobin value before administration of the first dose of study drug) at the treatment assessment endpoint (the screening Hgb was not used as the baseline).

Secondary Endpoints

- Mean change from baseline in bilirubin (excluding patients with Gilbert's syndrome) at the treatment assessment endpoint (defined as the mean value of Weeks 23, 25, and 26)
- Mean change from baseline in QOL, as assessed by the change in FACIT-F scale scores at the treatment assessment endpoint
- Mean change from baseline in lactate dehydrogenase (LDH) at the treatment assessment endpoint
- Number of transfusions and number of units after the first 5 weeks of study drug administration
- Mean change from baseline in hemoglobin at the treatment assessment endpoint

Exploratory Endpoints

- Time to first transfusion after the first 5 weeks
- Multiple endpoints considering QOL measures
- Incidence of solicited symptomatic anemia at EOT (end of treatment)

- Proportion of patients with hemoglobin level >12 g/dL at end of treatment
- Median time to normalization and proportion of patient with normalization of bilirubin, LDH, and haptoglobin
- Incidence of hemolytic breakthrough

Sample Size and Power Considerations

Approximately 20 patients with CAD who had a recent history of transfusion were planned to be enrolled (24 were actually enrolled). The sample size estimate was based on prediction of a true responder rate of 66% with a minimum responder rate of 30% required for success. With 20 patients, there was 90% probability that the lower limit of the 95% CI would be ≥30%.

Analysis Populations

- Full analysis set (FAS) included all patients who received at least 1 dose (including a partial dose) of study drug. The efficacy analysis was performed on the FAS.
- Per-protocol (PP) set included a subset of FAS patients who did not have any important protocol deviations impacting efficacy assessments.
- Safety analysis set included patients who received at least 1 dose (including a partial dose) of study drug.
- PK analysis set included all patients who received at least one dose of study drug and had at least 1 evaluable sample for baseline and PK concentrations.
- PD (pharmacodynamic) analysis set included all patients who received at least one dose of study drug and had at least 1 evaluable sample for baseline and PD concentrations.

Analyses of the Primary Efficacy Endpoint

Efficacy analyses were performed on the FAS. Each patient in the FAS population was classified as meeting the criteria of the primary endpoint (responder) or not meeting the criteria of the primary endpoint (non-responder). The 95% CI for the proportion of responders was calculated using the Clopper-Pearson exact method. Any patient withdrawing from the study prior to the Week 23 visit was considered a non-responder.

The primary analysis of the primary endpoint was based on the Composite Estimand, for which any missing response was considered a non-responder. Sensitivity analyses were carried out based on the Completer Estimand and the Per-protocol Estimand, respectively. Subgroup analyses for the primary endpoint were performed by age (<65 and ≥65 years), gender, baseline weight (<75 and ≥75 kg), number of transfusions within 12 months prior to study entry (≤2, 3-4, >4), baseline hemoglobin level (<8.5 and ≥8.5 g/dL), and previous rituximab therapy and/or cytotoxic therapy (yes/no). For these analyses, if there were <5 patients in a category, the cutoff may have been modified to adjust the distribution.

Baseline Hgb values were used for the primary endpoint, and baseline was defined as the last Hgb level before sutimlimab was initially administered. All 24 patients had Hgb assessed at Baseline and Days -14, -28, and -42.

Patients were allowed to receive a transfusion(s) during the Screening/Observation Period prior to the first study drug infusion if medically indicated per the Investigator's discretion. However,

the baseline visit (and the first infusion of study drug) had to occur at least 7 days following the transfusion.

Table 3. Assessment Schedule

Study visit (week/day)	Screening/ Observation Period[a]	Baseline	Part A		Part B extension phase	ET/EOS/Safety Follow-up[b]
			Weeks 1–25	Week 26 (EOT)		
	Days -42, -28, and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after the last dose
Visit windows	±3 days	N/A	±2 days	±2 days	±2 days	±2 days
Hematology panel[h]	X	X	X	X	X	X
Coagulation panel[h]	X	X		X		X
Clinical chemistry panel[h]	X	X	X	X	X	X
Urinalysis[h]	X	X		X	X[l]	X
FACIT-Fatigue[q]		X	X	X	X[l]	X
PGIS[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
PGIC[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
SF-12[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
EQ-5D-5L[q]		X	X (Days 49, 91, and 133 only)	X	X[l]	X
Solicited symptomatic anemia	X (Day -42 only)	X	X	X	X	X
Study drug administration[i]		X	X		X	
ADAs against sutimlimab		X				X
PK samples[j]		X	X	X	X[l]	X
PD samples[h,j]	X[m]	X	X	X	X[l]	X
Disease-related biomarkers[h]	X	X	X[n] (Day 91 only)	X		
Prior and concomitant medications, including transfusions	X	X	X	X	X	X
Healthcare resource utilization	X	X	X (Days 21, 49, 77, 105, 133, and 161)	X	X[p]	X
Adverse events[k]	X	X	X	X	X	X

Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints (change from baseline in Hgb, bilirubin, LDH, and FACIT-Fatigue) were analyzed using the Mixed Model for Repeated Measures (MMRM) at the treatment assessment endpoint. Analyses were performed based on the Hypothetical Estimand and the De-facto Estimand, respectively. Additional sensitivity analyses were carried out using multiple imputations.

Of the 24 treated patients, twenty-two (91.7%) completed Part A [16 of 17 (94.1%) and 6 of 7 (85.7%) in the 6.5-g and 7.5-g groups, respectively] and 22 of the treated patients are continuing in Part B. Of the 2 patients who did not complete Part A, 1 patient in the 7.5-g group discontinued from the study due to death on Day 32 from a fatal treatment-emergent SAE of hepatic cancer that was diagnosed on Day 22 and 1 patient in the 6.5-g group discontinued due to a pretreatment SAE of polymyalgia rheumatica that started on Day -8.

Table 4. Patient Disposition

Disposition Status	Dose: 6.5g (N=17)	Dose: 7.5g (N=7)	Total (N=24)
Analysis Sets; n (%)			
Safety Analysis Set	17 (100)	7 (100)	24 (100)
Full Analysis Set	17 (100)	7 (100)	24 (100)
Per-protocol Set	16 (94.1)	6 (85.7)	22 (91.7)
Completion Status; n (%)			
Completed Part A	16 (94.1)	6 (85.7)	22 (91.7)
Discontinued Part A	1 (5.9)	1 (14.3)	2 (8.3)
Adverse event	1 (5.9)	0	1 (4.2)
Death	0	1 (14.3)	1 (4.2)

Source: Statistical Reviewer

Overall, patients had a median age of 71.5 years (range 55 to 85), and most patients were ≥65 years old (19, 79.2%) and female (15, 62.5%). Race and ethnicity were not reported for 18 patients, as this was not allowed under local laws. Of the 6 patients with race and ethnicity data; 3 were Asian, 3 were white, and none were Hispanic or Latino. Most of the patients were from Europe (17, 70.8%); 3 (12.5%) were from the US. This study utilized a weight-based dosing strategy. As specified per protocol, all patients in 6.5-g arm had baseline weight <75 kg and all patients in the 7.5-g group had baseline weight ≥75 kg.

Table 5. Demographic Characteristics (Full Analysis Set)

Demographic Characteristic	Dose: 6.5g (N=17)	Dose: 7.5g (N=7)	Total (N=24)
Age (years)			
Mean (SD)	71.8 (9.05)	70.1 (6.01)	71.3 (8.18)
Median	72.0	70.0	71.5
Min, Max	55, 85	63, 77	55, 85
Age Group (years), n (%)			
<65 years	3 (17.6)	2 (28.6)	5 (20.8)
≥65 years	14 (82.4)	5 (71.4)	19 (79.2)
Sex, n (%)			
Female	11 (64.7)	4 (57.1)	15 (62.5)
Male	6 (35.3)	3 (42.9)	9 (37.5)
Race, n (%)			
Asian	3 (17.6)	0	3 (12.5)
White	2 (11.8)	1 (14.3)	3 (12.5)
Black or African American	0	0	0
Not collected[1]	12 (70.6)	6 (85.7)	18 (75.0)

Demographic Characteristic	Dose: 6.5g (N=17)	Dose: 7.5g (N=7)	Total (N=24)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	5 (29.4)	1 (14.3)	6 (25.0)
Not collected[1]	12 (70.6)	6 (85.7)	18 (75.0)
Region, n (%)			
Europe	12 (70.6)	5 (71.4)	17 (70.8)
North America	2 (11.8)	1 (14.3)	3 (12.5)
Asia	3 (17.6)	0	3 (12.5)
Other	0	1 (14.3)	1 (4.2)

[1] Data on race and/or ethnicity were not collected because of local regulations.
Source: Table 8 of applicant's CSR and confirmed by statistical reviewer

Primary Endpoint Analysis

Among the 24 patients in the Full Analysis Set, 13 patients met the responder criteria for the composite primary endpoint; the lower bound of the 95% CI of the response rate was >30% (54.2%, 95% CI: 32.8% to 74.4%), a predefined efficacy threshold.

Seventeen (70.8%) patients remained transfusion-free from Week 5 to Week 26 and no patient received a prohibited CAD medication. At the treatment assessment endpoint, 9 (37.5%) patients had normalized hemoglobin (≥12 g/dL), 15 (62.5%) patients had a ≥2-g/dL increase in hemoglobin, and 15 (62.5%) patients had either a ≥2-g/dL increase or normalization of hemoglobin.

Table 6. Summary of Primary Endpoint (Full Analysis Set)

	N=24
Response Rate	
n (%)	13 (54.2)
95% CI	32.8, 74.4
Components of the Primary Endpoint	
Subjects with either Hgb >=12 g/dL or increased >=2 g/dL from baseline at treatment assessment timepoint, n (%)	15 (62.5)
Subjects with Hgb >=12 g/dL at treatment assessment timepoint, n (%)	9 (37.5)
Subjects with Hgb increased >=2 g/dL from baseline at treatment assessment timepoint, n (%)	15 (62.5)
Subjects free of transfusions during Week 5 to Week 26 (EOT), n (%)	17 (70.8)
Subjects receiving no protocol prohibited CAD medications during Week 5 to Week 26 (EOT), n (%)	22 (91.7)

Source: Statistical Reviewer

The secondary endpoints are summarized below. The laboratory parameters are related to the primary endpoint and will be described in labeling. (b) (4)

(b) (4)

Table 7. Summary of Change from Baseline in Bilirubin (µmol/L) at Treatment Assessment Timepoint – Full Analysis Set

	N=14
Baseline mean	55.3
Mean at assessment timepoint	15.5
LS Mean for change from baseline, 95% CI	-38.2 (-42.5, -33.8)

Source: Statistical Reviewer

Table 8. Summary of change from baseline in FACIT-Fatigue score at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	31.2
Mean at assessment timepoint	44.3
LS Mean for change from baseline, 95% CI	10.9 (8.0, 13.7)

Table 9. Summary of change from baseline in lactate dehydrogenase (U/L) at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	424
Mean at assessment timepoint	301
LS Mean for change from baseline, 95% CI	-126 (-218, -35)

Source: Statistical reviewer

Table 10. Summary of Transfusions by Study Period – Full Analysis Set

Number of transfusions per subject	**Before Week 5 (n=24)**	**Week 5 to Week 26 (n=23)**
0	19 (79.2)	17 (70.8)
1	3 (12.5)	3 (12.5)
2	2 (8.3)	1 (4.2)
3	0	1 (4.2)
4	0	0
≥ 5	0	1 (4.2)

Source: statistical reviewer

Table 11. Summary of change from baseline in hemoglobin (g/dL) at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	8.45
Mean at assessment timepoint	11.63
LS Mean for change from baseline, 95% CI	2.60 (0.74, 4.46)

Source: statistical reviewer

8. Safety

The safety analysis for sutimlimab was focused on the primary safety population, which consisted of 34 patients with CAD from the following studies; BIVV009-01 Part C and Part E (N=10) and BIVV009-03 Part A and B (N=24). Studies BIVV009-01 Part E and BIVV009-03 Part B were ongoing at the time of this report. The primary safety population consisted mostly of patients with CAD (88%), a few patients with CAS (8.8%), and one patient with mixed CAD/WAIHA (2.9%). Given that the size of the primary safety population was small, supportive safety populations were also included. This included 32 patients with other CMDs (AMR, WAIHA, BP, ITP) and 96 normal healthy volunteers (NHVs). The data cut-off date for the primary CAD safety database was July 11, 2019.

Table 12. Primary CAD Safety Population Completion Status

	BIVV009-01		BIVV009-03		Total N=34 n (%)
	Part C N=10 n (%)	Part E N=4 n (%)	Part A N=24 n (%)	Part B N=21 n (%)	
Completion status					
Completed	10 (100)	0 (0)	22 (91.7)	0 (0)	7 (20.6)
Ongoing	0 (0)	3 (75)	0 (0)	21 (100)	24 (70.6)

Source: Derived from Applicant's SCS

A total of 162 patients or subjects (34 patients with CAD or CAS, 32 patients with other CMDs, and 96 NHVs) were treated with sutimlimab. An additional 27 patients with CAD were treated on an ongoing study (BIVV009-04) that remains blinded (not included in Table XX). Twenty-two subjects were treated with placebo. In the entire safety population, the median number of sutimlimab administrations was 4 (range 1 to 48). The median duration of exposure was 5.1 weeks (range 2.1 to 90.3). The total median dose was 17.1 g (range 0-275).

Table 13. Sutimlimab Exposure in the Safety Populations

	CAD Population N=34	NHV Population N=96	CMD Population N=32	Total N=162
Total number of administrations Median, (range)	20 (2, 48)	1 (1, 4)	5 (2, 26)	4 (1, 48)
Duration of study treatment (weeks) Median, (range)	38.4 (3.1-90.3)	2.1 (2.1-7.1)	5.3 (2.3-53.6)	5.1 (2.1-90.3)
Total Dose (grams) Median (range)	143.8 (14-275)	5.8 (0-32)	20.4 (5-170)	17.1 (0-275)

Source: Derived from Applicant's SCS

In the primary safety population, the median number of administrations was 20 (range 2-48) and the median total dose was 143.8 g (range 14-275). Overall the median duration of exposure was 38.4 weeks (range 3.1-90.3), with the majority of patients (19/34; 55.9%) exposed for ≥35 weeks and 10/34 (29.4%) patients exposed for ≥55 weeks.

Deaths

There were two deaths in the clinical development program. There was 1 death out of 34 patients (2.9%) in the primary safety population due to progressive hepatic cancer. In addition, there was 1 death in the supportive patient population in a patient with bullous pemphigoid who died due to cardiac failure. These deaths are not deemed to be drug-related.

Primary Safety Population

Two of the 34 (5.9%) patients in the primary safety population discontinued treatment. One patient died from hepatocellular carcinoma that was diagnosed after only two doses of sutimlimab, and one patient discontinued due to polymyalgia rheumatica, which was diagnosed prior to exposure to sutimlimab. Neither discontinuation was likely related to sutimlimab.

Table 14. Dropouts and Discontinuations in the Primary CAD Safety Population

	BIVV009-01		BIVV009-03		Total
	Part C N=10	Part E N=4	Part A N=24	Part B N=21	N=34
Discontinued prematurely	0 (0)	1 (25)	2 (8.3)	0 (0)	3 (8.8)
Adverse event	0 (0)	1 (25)	1 (4.2)	0 (0)	2 (5.9)
Death	0 (0)	0 (0)	1 (4.2)	0 (0)	1 (2.9)

Serious TEAEs occurred in 35% of the 34 patients of the primary safety population and 25% of 24 patients within the pivotal study. The most frequent SAEs in the primary safety population included sepsis (8.8%), bacterial infection (5.9%), bleeding (5.9%), cholecystitis or cholelithiasis (5.9%), malignancy (5.9%) and anemia (5.9%). The events of malignancy and anemia were related to underlying pathologies and are likely not adverse reactions.

SAEs

Serious TEAEs occurred in 35% of the 34 patients of the primary safety population and 25% of 24 patients within the pivotal study. The most frequent SAEs in the primary safety population included sepsis (8.8%), bacterial infection (5.9%), bleeding (5.9%), cholecystitis or cholelithiasis (5.9%), malignancy (5.9%) and anemia (5.9%). The events of malignancy and anemia were related to underlying pathologies and are likely not adverse reactions.

In total, 13 out of 34 (38.2%) of patients in the primary safety population experienced at least 1 Grade 3 (severe) TEAE. The most common (occurring ≥5% of the total population) TEAEs Grade ≥3 are shown in Table 14.

Table 15. Most common (>5%) TEAEs Grade ≥3 in the Primary Safety Population

FDA Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection, all*	2 (20%)	5 (20.8%)	7 (20.6%)
Sepsis	1 (10%)	2 (8.3%)	3 (8.8%)
Infection, bacterial	0 (0%)	2 (8.3%)	2 (5.9%)
Bleeding*	0 (0%)	2 (8.3%)	2 (5.9%)
Anemia	0 (0%)	2 (8.3%)	2 (5.9%)

Source: FDA clinical reviewer

*The following terms were combined

Bleeding includes: gastrointestinal hemorrhage, vitreous hemorrhage

Infection, all includes: urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, Escherichia sepsis, cholecystitis acute, respiratory tract infection, viral infection

Sepsis includes: pulmonary sepsis, streptococcal sepsis, Escherichia sepsis

The most common TEAEs (closely related terms were grouped) reported in >20% the primary safety population included respiratory tract infections, UTI, and fatigue. In the pivotal study BIVV009-03 Part A, the most common TEAEs by FDA MedDRA Query reported in >10% of the population were respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema.

Table 16. Most Common (>10%) Treatment Emergent Adverse Events in the Primary CAD Safety Population

Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection	**4 (40%)**	**16 (66.7%)**	**20 (58.8%)**
Respiratory tract infection*	4 (40%)	7 (29.2%)	11 (32.4%)
Urinary tract infection*	2 (20%)	5 (20.8%)	7 (20.6%)
Infection, viral*	2 (20%)	4 (16.7%)	6 (17.6%)
Nasopharyngitis	4 (40%)	2 (8.3%)	6 (17.6%)
Infection, bacterial*	2 (20%)	3 (12.5%)	5 (14.7%)
Vascular disorders			
Systemic hypertension*	0 (0%)	6 (25%)	6 (17.6%)
Hematoma*	2 (20%)	3 (12.5%)	5 (14.7%)
Bleeding*	0 (0%)	3 (12.5%)	3 (12.5%)
General disorders and administration site conditions			
Fatigue*	3 (30%)	4 (16.7%)	7 (20.6%)
Peripheral edema	2 (20%)	3 (12.5%)	5 (14.7%)
Pyrexia*	1 (10%)	3 (12.5%)	4 (11.8%)
Gastrointestinal disorders			
Abdominal pain*	2 (20%)	4 (16.7%)	6 (17.6%)
Diarrhea	1 (10%)	5 (20.8%)	6 (17.6%)
Nausea	3 (30%)	2 (8.3%)	5 (14.7%)
Constipation	2 (20%)	2 (8.3%)	4 (11.8%)
Dyspepsia*	1 (10%)	3 (12.5%)	4 (11.8%)
Gastroenteritis	1 (10%)	3 (12.5%)	4 (11.8%)
Nervous system disorders			
Dizziness*	5 (50%)	1 (4.2%)	6 (17.6%)
Headache	2 (20%)	2 (8.3%)	4 (11.8%)
Blood and lymphatic system disorders			
Anemia	1 (10%)	4 (16.7%)	5 (14.7%)
Musculoskeletal and connective tissue disorders			
Back pain	4 (40%)	1 (4.2%)	5 (14.7%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (10%)	4 (16.7%)	5 (14.7%)
Injury, poisoning and procedural complications			
Fall	1 (10%)	3 (12.5%)	4 (11.8%)

Source: FDA clinical reviewer

*The following terms were combined:

Abdominal pain includes; abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness

Bleeding includes; gastrointestinal hemorrhage, epistaxis, vitreous hemorrhage

Dizziness includes; dizziness, vertigo, balance, disorder, Meniere's disease

Dyspepsia includes; abdominal pain upper, dyspepsia

Fatigue includes; fatigue, asthenia, malaise, mental fatigue

Hematoma includes; hematoma, traumatic hematoma, vessel puncture site hematoma

Infection, **bacterial** includes; urinary tract infection bacteria, bacteremia, streptococcal sepsis, wound infection, staphylococcal, Escherichia sepsis, cystitis bacteria

Infection, viral includes; herpes zoster, oral herpes, respiratory tract infection viral, viral infection
Pyrexia includes; pyrexia, fever
Systemic hypertension includes; hypertension, essential hypertension, blood pressure increased
Upper respiratory infection includes; nasopharyngitis, respiratory tract infection, influenza like illness, viral upper respiratory tract infection, upper respiratory tract infection
Urinary tract infection includes; urinary tract infection, cystitis, cystitis bacterial

Infections are of particular concern for patients with CAD as they may exacerbate hemolysis. As the classical complement pathway is part of the innate immune system, it is possible that sutimlimab may increase the risk of non-serious and serious infections. Infections occurred in 58.8% of the 34 patients in the primary safety population and 58.3% of the 24 patients in the pivotal study.

Given its mechanism of action, sutimlimab may predispose patients to infections with encapsulated organisms. The complement system plays important roles in the recognition and elimination of pathogens through direct killing and/or phagocytosis. Direct killing of gram negative bacteria is done thorough the membrane attack complex (C5b-9). Gram positive bacteria and fungi tend to be resistant to the membrane attack complex. Sutimlimab does not inhibit the alternative complement pathway, therefore this function may remain intact. In general, over 50% of complement deficient patients experience severe infections, mostly caused by encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*.

Infections with encapsulated organisms occurred. In total, 3 of 34 (8.8%) patients in the primary safety population had an infection with an encapsulated organism. These included infections such as *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Staphylococcal epidermidis*. In addition, one patient in the 90-day safety follow up report from study BIVV009-03 Part B developed *Streptococcus pneumoniae* bacteremia, despite receiving a vaccination. There were no meningococcal infections or events of meningitis. Patients did not receive prophylaxis for meningococcal infections but they were required to have a vaccination for Neisseria meningitis. *Streptococcus pneumonia* and *Haemophilus influenzae* vaccinations were also required for study entry.

Even more relevant to sutimlimab, patients with inherited complement deficiencies in the classical complement pathway (including C1s) are at increased risk for encapsulated bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* and these particular infections were evaluated in this review. Although there are important differences between the inherited complement deficiency of C1s and those acquired by pharmacologic suppression, infections with encapsulated bacteria are nevertheless relevant for sutimlimab, and the risk should be communicated to patients and providers. Serious infections including, increased susceptibility to encapsulated bacteria, will be included in the Warnings and Precautions of the USPI. Patients should be closely monitored for infection, and suspected infections warrant immediate intervention. Vaccinations will be recommended for encapsulated bacteria. and it will be noted that although vaccination will likely decrease the risk of infection, it will not prevent it.

Following the 90-day safety update, one patient who received required vaccinations developed pneumococcal sepsis. This was the only case of a patient developing an infection of a vaccinated

encapsulated bacteria. Overall, bacterial and viral infections occurred at similar frequency, fungal infections were less common. No patient died or discontinued therapy due to infections.

Infusions reactions occurred in 2 out of 34 (5.9%) patients in the primary safety population and in one out of the 32 (3.1%) patients with CMDs. There were no events of anaphylaxis. Sutimlimab dosing was interrupted but not discontinued.

There is a theoretical risk that inhibition of the classical complement pathway may increase the risk of development of autoimmune disease, in particular SLE. During the study there were no clear trends of autoantibody positivity or clinical symptoms of SLE. There was one patient who experienced arthralgias during the study and developed a positive ANA after exposure to sutimlimab. This case was confounded by the patient's history of polymyalgia rheumatica and arthralgias prior to exposure to sutimlimab, and ultimately the ANA reverted back to negative. The risk of autoimmune development is difficult to assess given the small patient population and lack of long-term data; therefore, a PMR will be issued to continue to assess autoimmune disease development and/or worsening through a patient registry.

Safety Summary

In summary, sutimlimab was well tolerated and had low rates of discontinuations and deaths, in an older population with multiple comorbidities and concomitant medications. The relatively high incidence of AEs and SAEs is therefore not unexpected. The most common SAEs associated with sutimlimab were infections; in most cases, these were manageable with screening and aggressive supportive care. There is potential increased risk for infections with encapsulated organisms, in particular *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. This risk can be adequately described in the prescribing information. Overall the safety profile is acceptable for patients with CAD. Uncertainties remain given the small sample size, lack of a placebo arm, and limited data on long-term outcomes, and it is possible that new safety signals will be revealed in ongoing studies and the postmarketing period. Therefore, a PMR was recommended to complete and submit the ongoing studies and a PMR was recommended to assess the risk of autoimmune disease and encapsulated organisms.

9. Advisory Committee Meeting

The application for sutimlimab was not referred to an FDA advisory committee because this application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment of Cold Agglutinin Disease. The application clearly provides substantial evidence of effectiveness, and there were no critical safety issues. In short, outside expertise was not deemed necessary to assist in our decision-making for this BLA.

10. Pediatrics

Cold Agglutinin Disease is a disease of adults and is rarely diagnosed in children, although there have been reports of CAD in adolescents described in the literature. It would be difficult to study symptomatic pediatric patients in a rigorous way. This indication has orphan drug designation, and the Applicant is exempt from required pediatric assessments.

11. Other Relevant Regulatory Issues

Substantial evidence of effectiveness is generally understood to mean two independent adequate and well controlled studies, each convincing on its own. FDA's 1998 Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," describes situations in which a single adequate and well-controlled multi-center study may provide evidence of effectiveness without supporting information from other adequate and well-controlled studies. FDA's 2019 draft Guidance for Industry, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," goes further, providing examples of clinical circumstances where additional flexibility may be warranted.

The CARDINAL study demonstrates that sutimlimab confers substantial benefit with increases in hemoglobin levels and reductions in RBC transfusions in symptomatic patients with CAD. Importantly, decreases in LDH and bilirubin levels are consistent with decreased hemolysis, and provide objective, mechanistic support for the efficacy findings. Improvements in these objective laboratory parameters to the extent observed in the study would be extremely unlikely to occur spontaneously in an untreated population with CAD. Thus, we believe that the single, baseline-controlled trial provides substantial evidence of effectiveness for this application, especially in light of the situation. As explained in FDA's 2019 draft guidance on evidence of effectiveness, flexibility is appropriate in the setting of this rare, serious, and chronic disease, especially given the critical unmet need for an FDA-approved therapy.

12. Labeling

Substantial changes were made to the proposed USPI. Changes recommended by the Agency have been communicated to the applicant. Labeling agreement was not reached and additional labeling negotiations did not occur because of the recommendation for a Complete Response for the application.

13. Postmarketing Recommendations

Discussions regarding postmarketing recommendations are ongoing at the conclusion of the review and final agreement has not been reached. (b) (4) , several PMRs remain under consideration by the Division.

The following PMRs were proposed by the clinical team:

PMR 1: Complete part B of study BIVV009-03, "A Phase 3, Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion." Include updated summary safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

PMR 2: Complete part E of study BIVV009-01, "Safety, Tolerability and activity of TNT009 in Healthy Volunteers and Patient with Complement-Mediated Disorders. A Single/Multiple

Ascending Dose Phase 1 Study." Include updated summary safety and efficacy analysis in the final clinical study report.

PMR 3: Complete Study BIVV009-04, "A Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BIVV009 in patients with primary Cold Agglutinin Disease without a recent history of blood transfusion." (b) (4) Include updated safety information and submit datasets at the time of final clinical study report submission.

PMR 4: Conduct a study to characterize the long-term safety (up to 5 years) of exposure to sutimlimab in patients with primary Cold Agglutinin Disease (b) (4) . Submit yearly safety follow-up data for a (b) (4) The final study report should include an integrated safety dataset and a summary of the major safety findings for all patients, including the development or worsening of autoimmune diseases and the development of serious infections, including encapsulated organisms.

The following CMC PMC was also recommended:

(b) (4)

14. Recommended Comments to the Applicant

The following language (taken from the OPQ executive summary) is proposed for the Complete Response Letter (text may be edited before insertion in the Complete Response letter):

During a recent inspection of the (b) (4) facility for this BLA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
11/13/2020 01:11:07 PM

ALBERT B DEISSEROTH
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